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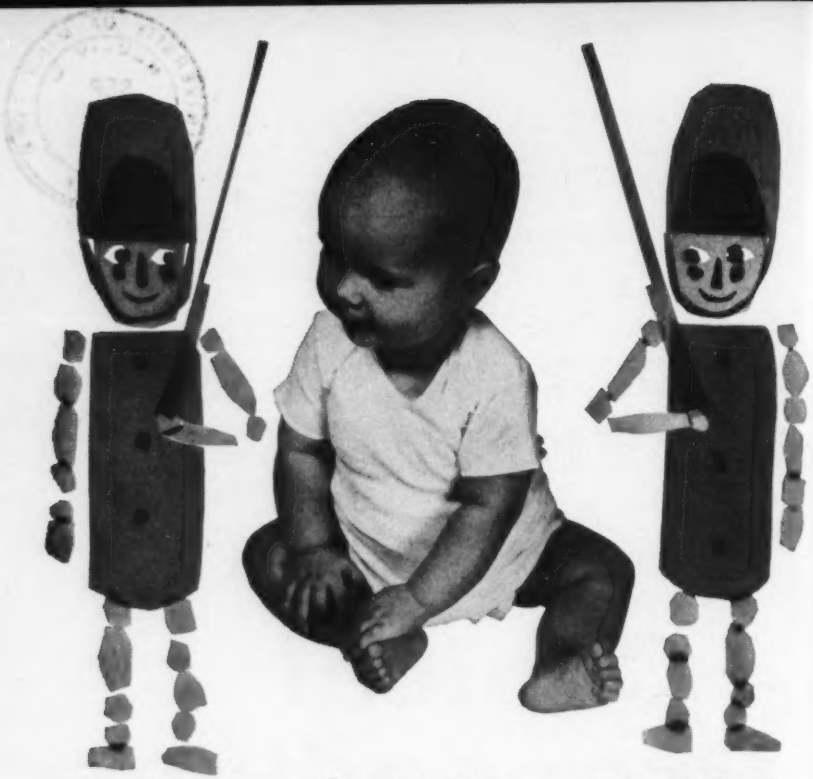

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(1) Diamond, L. K.; Smith, N. J., and Vaughan, V. C., III, in Nelson, W. E.: Textbook of Pediatrics, ed. 6, Philadelphia, W. B. Saunders Company, 1954, p. 962. (2) Nitzum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86:553, 1953.

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CHOLELITHIASIS AND CHOLECYSTITIS IN INFANCY AND CHILDHOOD

A Review

Walter E. Ahrens, M.D.*

INTRODUCTION

The signs and symptoms of cholelithiasis and cholecystitis are well known in the adult patient. These same signs and symptoms when present in an infant or child, however, frequently fail to arouse medical suspicion of the possibility of gall bladder disease. Potter's review in 1938 of such disease in children revealed that only 25 per cent were correctly diagnosed preoperatively, while 50 per cent of the cases were recognized at surgery and 25 per cent at autopsy[1]. Cases in older children and young adults are repeatedly reported as diagnosed gall bladder disease with histories of suggestive symptoms dating back to childhood. Why then is such a disease so frequently unrecognized or not diagnosed at an earlier age?

Several explanations are given. First, cholelithiasis and cholecystitis are uncommon diseases of infancy and childhood and therefore are unsuspected. Pertinent to this, a distinguished group of general surgeons was recently polled and 50 per cent had never seen gall bladder disease of this type in a child[2]. Secondly, gall bladder disease in children is often associated with either hemolytic disease or with systemic infection, and, consequently, the evidence of gall bladder disease may be misinterpreted. Finally, only recently has the pediatrician availed himself of certain diagnostic aids such as cholecystography and duodenal drainage which are so valuable in diagnosing adult gall bladder disease. In 1940 Seidler, et al. observed that only three cases of gall bladder disease in children had been recorded in which x-ray had established the diagnosis prior to surgery. He wisely predicted that with increased use of cholecystography in children, gall bladder disease would be recognized more frequently and at an earlier age[3].

The intent of this article is to refresh the minds of those engaged in pediatric care as to present knowledge concerning cholelithiasis and cholecystitis in infancy and childhood.

HISTORY

Gibson in 1722 is credited with first recording a case of gall bladder disease in a child[4]. The earliest recorded case of gall stones in an infant was described by Lieutaud in a 25 day old infant at autopsy[5]. More

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recently, Potter has popularized gall bladder disease in infancy and childhood by his reviews and discussions of 224 cases in 1928[6], and of 432 cases in 1938[1]. Ulin, et al. in 1952 reviewed both the literature and Potter's work and collected a total of 475 cases from 1722 to 1948. Of these he accepted only 326 cases which had actual gross or microscopic evidence of gall bladder disease[2]. Glenn, et al. in 1954 added an additional 30 cases[7]. In summary, there are at present less than 400 proven cases of gall bladder disease of infancy and children reported.

INCIDENCE

The actual frequency of gall bladder disease in children is unknown, but comparisons of the frequency of this disease in children and adults have been made. In one autopised series the comparative frequency of cholelithiasis as an incidental finding was 0.28 per cent in children 0-15 years[8], and 11.6 per cent in adults over 20 years of age[9]. At the Mayo Clinic, Walters reported an incidence of 1.3 children per 1000 adult cases of gall bladder disease.

Negroes, regardless of age, appear to have less gall bladder disease than do Caucasians. In one adult series cholecystitis was twice as common in Caucasians as in Negroes with incidences of 200 per 100,000 and 106 per 100,000 respectively[10]. Potter suggested that gall bladder disease was more frequent in the Caucasian child,[6], but gave no statistics. Since then, 43 children with cholecystitis have been reported in the period from 1938 to 1952, and only 3 were Negroes.

Regarding sex incidence, Potter as of 1938 reported that gall bladder disease was slightly more common in female children than in male children by a ratio of 54.4 per cent to 45.6 per cent[1]. In Ulin's series there was, however, a 3 to 2 ratio with male children having more gall bladder disease[2]. In either series, there is certainly not the marked predominance of 4 to 1 of female patients as seen in adult series[2].

If the pediatric group may be considered to range from neo-natal life to 15 years, gall bladder disease is more commonly diagnosed after the age of 8 years[1, 11]. Potter observed that there was an increasing incidence of such disease with age as follows:[1]

Fetal	2
Neo-natal	24
Infancy	65
1–5 years	56
5–10 years	109
10–15 years	136

ETIOLOGY, PATHOGENESIS

The etiology of gall bladder disease is no better understood in the child than it is in the adult. Certain observations and theories, however, deserve presentation.

Cholelithiasis occurs more frequently in children than does cholecystitis. Cholelithiasis and cholecystitis are not so commonly associated in children, 57–69 per cent, as in adults, 80–95 per cent[2]. Ulin suggests that chronicity of adult gall bladder disease may be responsible for this apparent difference[2]. The most common cause of cholelithiasis in children is hemolytic disease with abnormally high rates of red blood cell destruction and excretion of hemoglobin pigments through the biliary system[12]. Therefore, when confronted with cholelithiasis in a child, one should first rule out congenital hemolytic anemia if the patient is Caucasian and sickle cell anemia if Negro. Gross reported that 3 of his 6 patients with cholelithiasis had hemolytic anemias[12]. The Mayo Clinic noted that 70 per cent of its patients with congenital hemolytic anemia had associated stones[13].

In a recent study of 21 Negro children with sickle cell anemia, Mintz, et al. observed a 9.5 per cent incidence of cholelithiasis[14] which was comparable to an autopsied series of Wein in which 10.5 per cent of the sickle cell anemia cases between the age of 1 day and 20 years had stones[15]. Wein's statistics in abstract are as follows:[15]

Age	No. of patients	No. with cholelithiasis
0–10 yr.	12	0
11–20 yr.	9	2
21–30 yr.	13	5
31–40 yr.	5	5

In view of the comparative rarity of gall bladder disease in Negroes, one might justly conclude that Negro adolescents and young adults, who have gall stones, probably have sickle cell disease as well.

There is, however, a significant group of children with cholelithiasis who do not have hemolytic anemias. It is postulated that any condition that produces biliary stasis may produce stones. Conditions implicated include congenital anomalies of the extrahepatic system, infection of the gall bladder, spasm of the ampulla of Vater, extrinsic pressure on the extrahepatic system, or inflammation about the common duct.

Seidler, et al. suggest that gallstones of the infant should arouse suspicion of a congenital anomaly of the extrahepatic system[3]. Recently Forshall, et al. reported 5 children with cholelithiasis of whom 3 had anomalies of the cystic duct and none had hemolytic disease[16].

The manner in which infection may produce stones in children is open

to much speculation. Non-specific factors of dehydration and anorexia may be significant[7]. Agglutinins produced in response to specific infections may cause precipitations in the bile, forming niduses for stone growth[17]. Compression of the extrahepatic ducts by enlarged mesenteric nodes, particularly at the junction of the cystic and the common ducts, may be of particular importance in children[11]. An occasional case of pancreatitis has been described as a cause of extrahepatic obstruction and perhaps may be a factor in the formation of biliary stones[18].

Cholecystitis is most commonly associated with local or systemic infection in the child, but malnutrition, dehydration, and congenital anomalies have been implicated in a minority of cases. Of interest, Ulin would not accept in his series either cases of malnutrition or of a congenital anomaly of the biliary tract[2].

In a series of autopsies of malnourished Chilean infants, histologic findings interpreted as cholecystitis were observed in 35 per cent of routine autopsies of severely debilitated infants[19]. Cholecystitis may occur in association with neonatal sepsis or with gastro-enteritis in infancy, and perhaps such infection was a factor in these cases.

Among infections frequently quoted in past literature as significant in producing cholecystitis are infections of the upper respiratory tract, influenza, scarlet fever, and Salmonella. Considering the frequency of these infections and the rarity of cholecystitis in children, one might indeed be skeptical of their etiologic significance. Ulin studied 12,352 cases of scarlet fever and could find only two cases of possible cholecystitis, neither of which was confirmed pathologically[2]. Salmonella, particularly *S. typhosa*, in the late nineteenth and early twentieth centuries was much publicized as an important and frequent infecting agent in cholecystitis of both children and adults. Reid and Montgomery reported 18 cases of cholecystitis in children due to typhoid fever which were confirmed at surgery prior to 1920[20]. Fifteen of seventeen patients in Potter's series with acute cholecystitis, gangrene, and perforation were credited to *S. typhosa*[1]. In fact, in the 1930's cholecystitis, if not caused by Salmonella infection, deserved comment. Holbrook in 1934 reported a case of cholecystitis without stones and without a Salmonella infection and could collect only 27 similar cases from the literature[21].

More recently, the incidence of typhoid has been reduced by use of antibiotics and, perhaps of even greater importance, by public health measures. Although Salmonella infections are still a relatively common problem, cholecystitis in children due to this organism is quite rare. Bonta, et al. in 1952 for this reason described a case in a 4 year old child from whom *S. oranienberg* was cultured first from the stool and later from the gall bladder at surgery for cholecystitis[22]. In contrast to past opinions, Sal-

monella cholecystitis in children today is rare as is evidenced by a series of 2000 cases of Salmonella infection. Only 10 of these cases had associated cholecystitis, and all 10 were adults[23]. Further, in a series of 44 cases of cholecystitis recorded by the National Salmonella Center of New York City, the youngest case reported was 16 years old[24].

Some authors have stressed not the organism but the locus of infection as of particular significance. Snyder and Farr have each proposed that cholecystitis may occur as a metastatic complication of a chronic or subacute infection of the appendix[25, 26].

Two parasites have been implicated in gall bladder disease in children: *Giardia lamblia* and *Ascaris lumbricoides*[27].

By means of biliary drainages Smithies, Zelditch, et al., among others, have recovered Giardia concurrently with symptoms considered to be due to cholecystitis[28, 29]. This parasite could not be recovered by drainage when symptoms were relieved during treatment. Giardia was found in quantity in those gall bladder specimens removed in surgical treatment. Zelditch, et al. in a series of 32 children with cholecystitis found Giardia in 12 biliary drainages[29]. Golob believed that Giardia could simulate acute cholecystitis by obstructing the cystic duct[30]. Not all authors have agreed, however, on the pathogenicity of Giardia in acute cholecystitis or suggestive symptoms thereof[31, 32]. Undoubtedly Giardia, when present in the gall bladder, is also present in large quantity in the small bowel and may produce an enteritis of perhaps greater clinical significance than the gall bladder infestation. Also Giardia infestations can occur without clinical symptoms.

In general, Ascaris infestations have been much less publicized as being of a pathogenic significance in gall bladder disease in children. There is one report, however, of an Ascaris as a constituent of a stone in the ampulla of Vater[33].

CLINICAL FEATURES

The signs and symptoms of gall bladder disease are in many respects similar in children and adults. The similarities and differences deserve mention.

Nausea, vomiting, and constipation are common symptoms. Dietary intolerance to fatty foods and chronic "dyspepsia" are, however, rarely described in children. Abdominal pain is a frequent presenting complaint in the child but pain localization may be either vague or localized to the epigastrium, to the right upper quadrant, or to the umbilicus. Referral of pain to the back or to the shoulder is uncommon. Fever and toxic signs are more often associated with acute cholecystitis.

Right upper quadrant abdominal spasm or guarding in cholecystitis

appears to be common. Jaundice is a confusing sign and is more commonly seen in gall bladder disease of children than in adults. As might be expected, cases of cholecystitis have been confused with infectious hepatitis. An estimated 26 to 45 per cent of the children have a present or past history of jaundice in contrast to a mere 8 to 10 per cent of adults[2].

Gall stones in children are most frequently bilirubin pigment stones. This is significant because such stones are not radio-opaque and can not be visualized by a scout abdominal x-ray until calcium has also been deposited in the stone. On cholecystography non-calcified pigment stones are seen as radiolucent shadows in the gall bladder.

Of importance, common duct stones are less frequent in children, 6 per cent as compared to 17 per cent in adults[2]. In those cases with associated jaundice 92 per cent of the children had no common duct stones[2] as compared to 53 per cent of the adults[34]. The jaundice of a child with cholecystitis, therefore, is more frequently considered due to common duct obstruction of an inflammatory nature, e.g. nodes compressing the common duct or to pancreatitis, than to a stone.

Cholecystitis in the child presents more frequently than in the adult the picture of an acute infection with microscopic evidence of infiltration of polymorphonuclear leukocytes and bacteria in the mucosa[2].

Primary gall bladder malignancy has been described in 2 of the 326 cases of gall bladder disease in children accepted by Ulin, a 0.6 per cent incidence as compared with a 1–3 per cent incidence in the adult[2].

The differential diagnosis of gall bladder disease in children can include a number of illnesses. Perhaps the most common misdiagnoses of proven cases of gall bladder disease are appendicitis, intestinal obstruction, and infectious hepatitis. One must also consider pneumonia, renal disease, perforated viscus, perinephric abscess, diaphragmatic abscess, pancreatitis, peptic ulcer, duodenitis, and pericarditis.

As might be expected, gall bladder disease of infancy may be particularly difficult to recognize. Snyder reports a case in which an abdominal malignancy was first suspected because of ascites. Actually perforation of the gall bladder had occurred with subsequent bile peritonitis[35].

Glenn had one case originally considered to be anorexia nervosa in an older child[7].

Two uncommon diseases of the gall bladder that may be extremely difficult to differentiate from cholecystitis or cholelithiasis are acute distension of the gall bladder and torsion of a floating gall bladder. Both Rankin and Gross independently have recently encountered two cases of acutely distended gall bladders. Both authors suggested that cystic duct compression by mesenteric adenopathy might produce this condition[36, 37].

One must be accurate and careful in diagnosing cholecystitis in the

jaundiced child, since infectious hepatitis is admittedly the more common disease. Certainly conservative therapy is indicated if in doubt, in view of the increased risk of surgery if infectious hepatitis is present[2].

It should be emphasized that one should not consider every vague abdominal pain of children to be due to gall bladder disease. Routine cholecystograms were performed in an extensive outpatient study of 95 children with chronic, vague, abdominal pains, and in that series the only significant finding was one non-filling gall bladder[38].

Diagnostic studies after a suggestive history and physical examination should include a "scout" x-ray of the abdomen, duodenal drainage, and an oral or intravenous cholecystogram. Blood dyscrasias and hepatocellular disease must be ruled out or recognized. As previously mentioned, a "scout" x-ray is of value if the gall stones are calcified and, even if no stones are present, may reveal an abnormally large gall bladder shadow that can be distinguished from the liver edge. Duodenal drainage is of considerable value in adult studies and is applicable to children. A jutte tube can be introduced into the duodenum and a few cc. of 25 per cent magnesium sulfate injected to stimulate the flow of bile. The drainage returns should then be examined for mucus, floccules, leukocytes, parasites, or cholesterol crystals in "B" or gall bladder bile by a trained observer[27]. Cholecystography as described by Harris and Caffee would appear to be somewhat unpredictable in the child under 3 years of age. They successfully performed cholecystograms in only 15 out of 27 children of this age group. Only 6 of 12 infants under the age of 6 months had gall bladders visualized[39]. This report emphasizes the pitfall of diagnosing either disease or congenital absence of the gall bladder by failure to concentrate dye on a single cholecystogram. Mintz, et al. in 1955 were more optimistic with 20 of 21 cholecystograms successfully performed and claimed uniformly good results under the age of 3 years[14].

Successful treatment of gall bladder disease in children depends on judicious use of either or both antibiotic therapy and surgery. Since the pathology of acute cholecystitis is that of an acute bacterial infection, antibiotics may suffice. Indeed, Bonta, et al. have noted a decrease in the number of recorded cases of acute cholecystitis in children in the period of 1942–52 and speculate that this is a result of the advent of antibiotic therapy in the management of acute abdominal diseases of the child[22]. Surgery is indicated whenever the local signs of infection are not controlled by antibiotics alone. The degree of edema at the neck of the gall bladder may dictate discretion and the more conservative cholecystotomy as the procedure of choice[12].

If cholelithiasis is present, the surgeon may perform a cholecystectomy if there is also evidence of cholecystitis. If the stones are the result of a

hemolytic anemia and no infection is present, one may elect to remove only the stones. Of interest, Snyder, et al. report successful surgery on a 6 week old infant with stones of both the gall bladder and of the common duct. The common duct was successfully flushed with a 19 gauge polyethylene tubing and a syringe[35]. Both Ulin and Glenn independently consider that common duct exploration is not a mandatory procedure in children unless obvious biliary obstruction is present[2, 7].

In the surgical management of a patient with congenital hemolytic anemia, Gross warns of the increased risk incurred if both cholecystectomy and splenectomy are performed at the same operation. Separate surgical procedures are recommended with splenectomy performed first, unless common duct obstruction with calculi is seriously considered[12].

Adrenal corticosteroids have been used in a single case of cholecystitis and cholelithiasis described by Dannenberg, et al., and in that case were considered a life saving supplement to antibiotic therapy as the child was evaluated as too critical for any surgery[40].

SUMMARY

A review of the recent literature concerning cholecystitis and cholelithiasis of infancy and childhood has been presented. Although an uncommon disease in this age group, there is a definite clinical picture which should arouse suspicion by history and physical examination and which may be confirmed by a few readily available diagnostic tests.

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GALL BLADDER DISEASE IN CHILDREN

Four Case Reports

Walter E. Ahrens, M. D.*

Cholelithiasis and cholecystitis are uncommon diseases of infancy and childhood. Less than 400 cases of such disease, pathologically confirmed, have been reported in the literature as of 1954[1, 2]. There has been no past recorded experience with these diseases at this hospital. Within the past year and a half, however, four children have been diagnosed as having probable gall bladder disease and have had cholecystectomies with pathologic examinations of the surgical specimens. Although only three of these four children had demonstrable gall bladder disease, all cases will be summarized for the purpose of contrasting patients with and without gall bladder disease by history, physical examination, and laboratory studies.

Case 1

C. J. H., a 7½ year old negro girl, with known sickle cell anemia was admitted to Children's Hospital of D. C. in April, 1956, with the complaint of intermittent periumbilical pain of two months duration.

Her blood dyscrasia was first diagnosed at the age of 15 months. Transfusions had been given on 11 of her 16 previous admissions for crisis or infection.

Two months prior to this admission intermittent headaches, dizziness, weakness, periumbilical pain, constipation, and persistent scleral icterus developed. Despite repeated clinic visits and one hospitalization, no lasting relief could be given.

Both mother and child were known to psychiatric and social service personnel as emotionally labile persons. The mother is overprotective, and in past crises the girl had responded dramatically when the mother had left the ward.

X-ray examination of the abdomen two weeks prior to admission showed four calcified densities in the right upper quadrant. A cholecystogram was performed, and a normally functioning gall bladder containing calculi was observed. The hemogram remained unchanged throughout this illness.

Although no fever, fatty food intolerance, vomiting, acholic stools, or localized abdominal signs were noted, cholecystectomy was finally considered in an attempt to relieve this child's symptoms.

When admitted for elective surgery, a pale, well-nourished negro girl in no distress was observed. The sclerae were icteric, and the mucous membranes were pale. An "innocent" systolic murmur was heard over aortic and pulmonic areas. The abdomen was soft and non-tender, with a smooth firm liver edge palpable one-finger breadth below the right costal margin. No other abdominal masses were noted. Routine neurologic tests were within normal limits.

Complete blood count and routine urinalysis were unremarkable except for this child's anemia with a hemoglobin of 7.7 gm. per 100 ml., a hematocrit of 23 per cent, and a leukocyte count of 12,600 per cu. mm.

After transfusion an uncomplicated cholecystectomy and appendectomy were performed.

* Assistant Chief Resident.

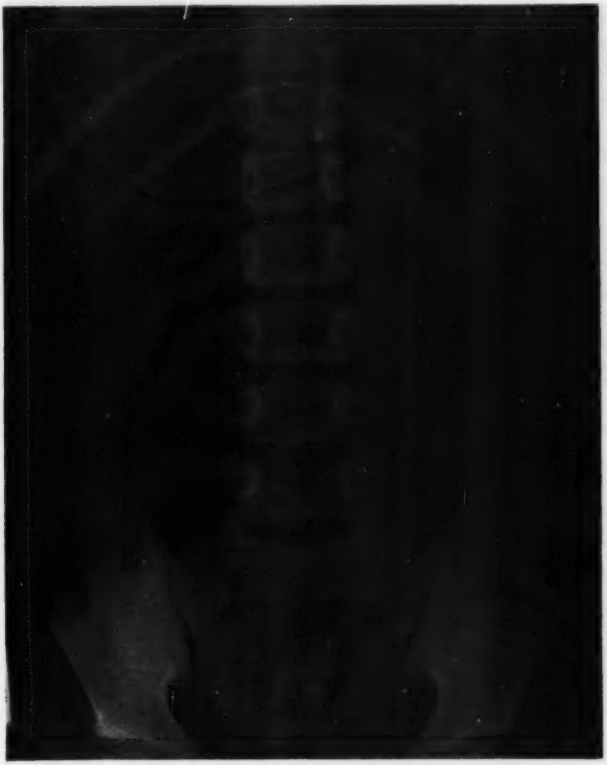

FIG. 1. Case 1. On flat plate of the abdomen 5 calcific shadows in chain-like formation are visualized in the right upper quadrant of the abdomen.

Post-operatively the patient had low grade fever for two days and on the fifth day a single generalized convulsion of 10–15 minutes duration. For four days after her seizure the patient had left leg and arm weakness with an increased left patellar reflex, left ankle clonus, and a weak left Babinski. Neurologic consultation suggested that a thrombosis of the right middle cerebral artery had occurred.

A detailed neurologic history at this time disclosed that the patient had had past episodes of dizziness, memory lapses, and day dreams during the past year. Skull x-rays were remarkable only for the demineralization of bones seen in severe chronic anemias. An electroencephalogram demonstrated the dysrhythmia characteristic of petit mal convulsive disorder. As anti-convulsant medication, phenobarbital and dilantin were subsequently given daily without further seizures.

Two weeks after discharge, there was one brief episode of mild abdominal distress when the mother was away from the child for a day, and this raised the question of re-referral to the psychiatric service. Subsequent to this, there were no symptoms

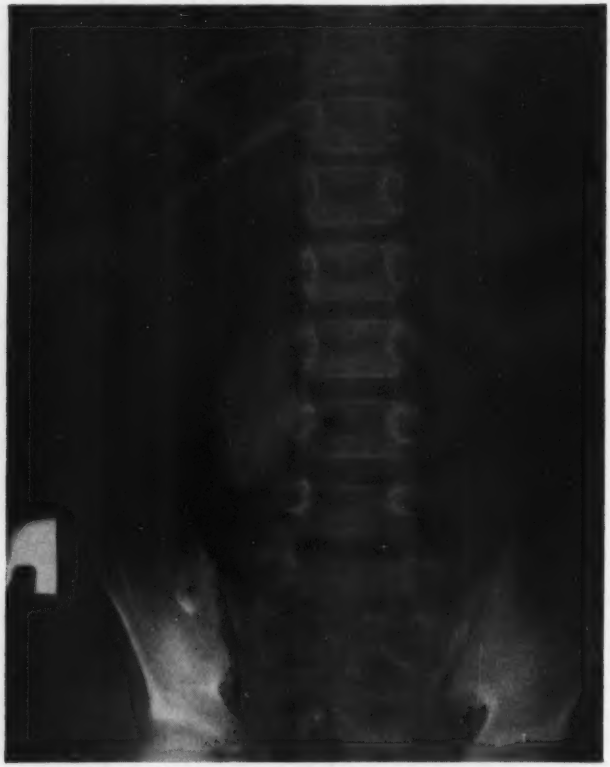

FIG. 2. Case 1. The calcific shadows are visualized in the fundus of the gall bladder during an oral cholecystogram. The dye was concentrated well and emptied well after a fatty meal.

for 3½ months and surgery appeared to have been beneficial. At this time anti-convulsants were stopped. Attacks of severe abdominal pain without fever, apparent infection, or hemolysis, occurred on the fifth and on the twentieth day after discontinuing anti-convulsant therapy. The second attack required hospitalization and analgesics.

Anti-convulsants were renewed, and the child has since been asymptomatic for two months.

The pathologic specimen of gall bladder was grossly normal except that it contained five black stones, the largest being 0.5 x 0.4 x 0.4 cm. in size, and much "sand". There was no microscopic evidence of cholecystitis or appendicitis. There were no palpable stones in the cystic or common ducts at surgery, and no probing or flushing of the ducts was performed.

Case 2

A. T., a 12 year old negro boy, with known sickle cell disease, was admitted to Children's Hospital of D. C. in October, 1956, for elective cholecystectomy. He had had 56 past hospital admissions with a total of 76 transfusions for repeated infection and crises since his first crisis at the age of 11 months.

He had a past history of recurrent abdominal and joint pains, joint swellings, epistaxis, hematuria and nocturia, recurrent respiratory infections, icteric sclerae, tiring easily and dyspnea on exertion.

An enlarged spleen was removed at age 3 years for possible hypersplenism. The intervals between transfusions were extended post-operatively from weeks to months, and he was considered to have benefitted from this procedure.

In May, 1955, while hospitalized, the boy had a complaint of right upper quadrant abdominal pain which radiated to his back. An x-ray of the abdomen at that time revealed right upper quadrant opacities. No functioning of the gall bladder could be demonstrated by oral cholecystography. With clinical improvement, however, he was discharged and followed in the hematology clinic.

In October, 1955, the opacities were again observed on an intravenous pyelogram which showed only downward displacement of the right kidney by an enlarged liver. Again no filling of the gall bladder was demonstrated on an oral cholecystogram.

The patient, although asymptomatic, was advised by a surgical consultant to have elective surgery in view of apparent cholelithiasis with a non-functioning gall bladder. There was no history of food intolerance and no gastro-intestinal symptoms or signs. Icterus, however, was persistent with an unchanged, moderately severe anemia.

On admission the boy had signs consistent with bronchopneumonia and had a blood dyscrasia. He had fever of 101°F with moderate respiratory distress. He had icteric sclerae, pale mucous membranes, dental caries, and generalized rales and expiratory wheezes throughout his chest. There was a grade II apical systolic murmur with a short palpable thrill at the apex. A smooth non tender liver edge was palpable 10 cm. below the right costal margin. There was minimal clubbing of the fingers and toes.

On admission urine analysis was normal, and the blood studies showed a hemoglobin of 5.3 gm. per 100 ml., a hematocrit of 15 per cent and a leukocyte count of 15,400 with 72 segmented and 6 band polymorphonuclear leukocytes. Total protein, albumin, globulin, and cholesterol values were within normal limits. Total bilirubin was 8 mg. per 100 ml. with direct 0.8 and indirect 7.2 mg. per 100 ml. Thymol turbidity was 1.8 units; cephalin flocculation was 4+ (48 hours), and alkaline phosphatase was 6.0 Bodansky units.

After treatment of his pulmonary infection, with clinical and radiographic clearing of bilateral pulmonary infiltrations, elective cholecystectomy, appendectomy, and liver biopsy were performed. The surgery was well tolerated, and the post-operative course unremarkable.

On surgical examination an impacted stone in the cystic duct with dilatation of this duct was observed. The gall bladder measured 9.0 x 2.0 x 1.0 cm. and had a smooth shiny hyperemic serosa. The lumen contained four dark green calculi, a moderate amount of yellow granular calculi, and bloody fluid. The mucosa was moderately hyperemic. Cholecystitis was not present microscopically. The appendix was normal. The liver biopsy was consistent with hemosiderosis and early biliary cirrhosis.

Case 3

D. L., a 3 year old white boy was admitted to Children's Hospital of D. C. for the second time in February, 1956, for control of intermittent Salmonella septicemia of 3½ months duration.

In September of 1955 the child first became ill with high fever, vomiting, and diarrhea. He then had three further hospitalizations for the same symptoms one to two weeks after hospital discharge.

In December, 1955, the child was first admitted to this hospital.

As previously, when antibiotics were discontinued symptoms recurred, and on admission he appeared acutely ill with fever spiking to 105°F, vomiting, diarrhea, pallor, and marked hepatosplenomegaly. Sepsis was demonstrated with six positive blood cultures for *Salmonella newport*, but no gastro-intestinal infection could be demonstrated despite repeated stool cultures. Therapy for two weeks with intravenous chloramphenicol followed by two weeks of oral neomycin and tetracycline was given with dramatic remission.

Despite multiple studies over a six week period no focus of the septicemia could be found. Significant findings were an elevated agglutination titer to Salmonella Group C of 1:320, aseptic necrosis of the right femoral head, and a non-filling gall bladder by oral cholecystography. Repeated chest x-rays, skeletal x-ray survey, a battery of liver function tests, an intravenous pyelogram, a lumbar puncture, an electroencephalogram, a bone marrow, and a repeat tuberculin skin test were normal. After remaining asymptomatic for two weeks with four negative stool and five negative blood cultures, the child was discharged.

Five days after discharge the child returned with an exacerbation of all previous signs and symptoms. Again blood cultures were positive and stool cultures negative for *Salmonella newport*.

In search of the focus of sepsis, the gall bladder was re-examined. A duodenal drainage was performed, but no abnormality of the returns was noted. By intravenous cholecystogram the gall bladder was not outlined (until after 1 hour), appeared enlarged 4–5 times normal size, concentrated dye well, showed little contraction to fatty meal, but emptied well within 24 hours.

Nevertheless, cholecystectomy was finally elected and performed without complication in February, 1956.

The surgical specimen showed no gross or microscopic evidence of cholecystitis and cultures of the bile were negative.

Sepsis, with Salmonella by blood culture, recurred in March, 1956, and again responded to chloramphenicol given intravenously.

Subsequent studies proved equally fruitless including a biopsy of the head of the right femur in search of osteomyelitis. The boy was finally discharged in June, 1956, on suppressive dosage of oral chloramphenicol with no focus of infection yet found.

Case 4

R. D., an 8 year old white boy entered the Children's Hospital of D. C. for his first admission in December, 1955, with complaint of fever and stiff neck for one day. His symptoms included fever, vomiting, headache, stiff neck, and eye pain of one to two days duration, and were increasing in severity since onset.

The only significant past illnesses were ascariasis treated seven months before admission and a sore throat untreated three weeks before admission.

On admission the boy was acutely ill, and disoriented. The temperature was

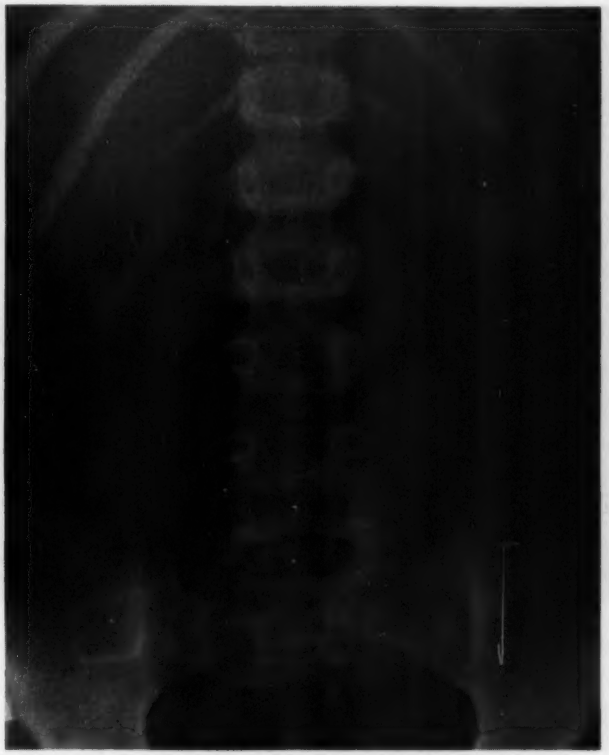

FIG. 3. Case 4. The flat plate of the abdomen revealed a saccular shadow in the right upper quadrant of the abdomen. This shadow displaced both hepatic flexure and transverse colon downward and was suggestive of an enlarged gall bladder.

104°, pulse 145, respirations 32, and blood pressure 120/60. There was a nonspecific maculo-papular rash of the hands. No other rashes were present. There was erythema of the conjunctivae and inflammation and exudates of both tonsils. Moderate cervical lymphadenopathy was present. Significant neurologic signs were marked neck and back stiffness, bilateral Kernig signs, and a neck Brudzinski sign.

Laboratory studies included: cloudy spinal fluid with 470 mg. per 100 ml. of protein and 5 mg. sugar per 100 ml., and a cell count of 8,000 per cu. mm. with a differential of 94 per cent polymorphonuclear and 6 per cent mononuclear cells; urine with 250 mg. of protein per 100 ml., and a microscopic sediment of 20–25 erythrocytes and 15–20 leukocytes, one granular cast and many bacteria per high power field; hemogram with 12.5 gm. of hemoglobin per 100 ml., 30,200 leukocytes, with a differential of 62 segmented and 11 band neutrophils. The blood urea nitrogen was 29 mg. per 100 ml. Blood, throat, urine, and spinal fluid were cultured, but no pathogens could be demonstrated subsequently after 48 hours.

Chloramphenicol 30 mg./kg. and tetracycline 15 mg./kg. intravenously every six

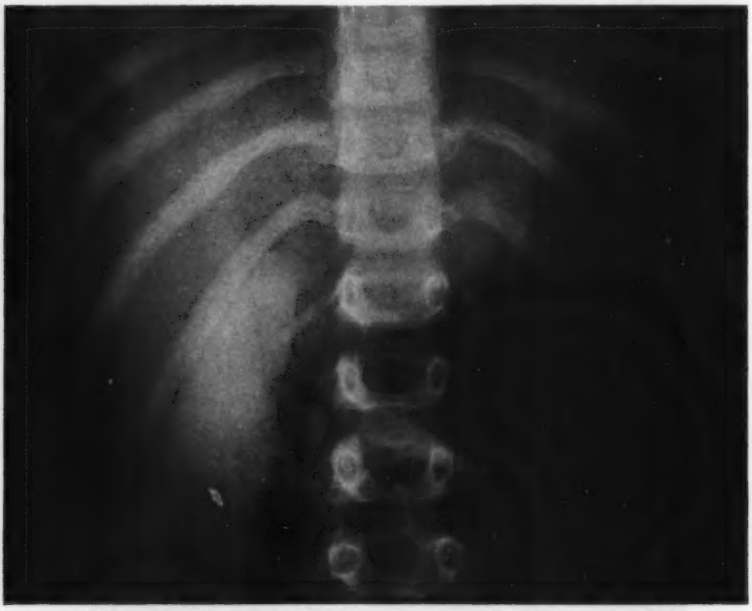

FIG. 4. Case 4. By intravenous cholecystography this shadow was outlined as a markedly dilated gall bladder. This x-ray was taken 96 hours after a fatty meal and demonstrated a pathologically functioning and markedly dilated gall bladder.

hours were given for 10 days. The spinal fluid showed marked clearing on the third day and fever subsided on the fourth day.

The course was marked, however, by persistent, severe vomiting. Melena was noted on the fifth day and probanthine® and chlorpromazine were added to the therapy. A possible neurological complication of subdural effusion was considered, but a normal electroencephalogram, spinal fluid, and neurologic evaluation made this improbable.

By the tenth day of persisting vomiting, definite melena, and questionable hematemesis, attention was directed to the abdomen. Right upper quadrant tenderness was present and the liver was palpable 2–3 cm. below the right costal margin. X-ray of the abdomen demonstrated a large saccular shadow in the right upper quadrant displacing the large bowel downward. Barium contrast x-rays of the upper gastrointestinal tract was unremarkable except for dilatation of the third portion of the duodenum and persistence of the saccular shadow.

On the eighteenth day an intravenous cholangiogram was performed. A large gall bladder was outlined in 18 hours and did not empty in 72 hours after a fatty meal. Urine culture repeatedly demonstrated *Staphylococcus aureus*; erythromycin was begun for probable persisting urinary tract infection. A normal intravenous pyelogram ruled out the probability of congenital anomaly or chronic infection of the kidneys and urinary tract.

Duodenal drainage was performed, but microscopic examination and culture were non-contributory.

With persistence of vomiting severe enough to require repeated parenteral fluids, however, cholecystectomy was finally elected and performed on the twenty-third hospital day.

The post-operative course was dramatic in that vomiting ceased. An uneventful recovery was observed. During convalescence stool examination revealed the presence of ova of Ascaris, Trichiuris, and *Endamoeba nana* for which the boy received piperazine citrate. A later urine culture was sterile.

The boy was discharged to a convalescent home, and the one and two month follow-up examinations were unremarkable. Subsequently he has returned to full activity and is without apparent residual of his illness.

The surgical specimen of gall bladder measured 9.0 x 2.0 x 2.0 cm., and had an injected, non-glistening serosa. There were no crystals or parasites and only 20 cc. of homogenous green bile. No mention was made of the presence of enlarged lymph nodes compressing either the cystic or the common ducts in the surgical report. The microscopic examination was rendered as "acute cholecystitis". The appendix was grossly normal with slight infection of the serosa diagnosed as peri-appendicitis.

DISCUSSION

Cases 1 and 2 illustrate the predilection for gall stones observed in children with hemolytic dyscrasias. These children had severe sickle cell anemia and had had repeated transfusions. Neither case demonstrated signs or symptoms of acute cholecystitis or of common duct obstruction. Case 2 had had an episode of pain referred from the abdomen to the right back some months prior to surgery, and his gall bladder could never be visualized by repeated cholecystography. At surgery he had cystic duct obstruction with a stone. No stones were palpable in the common ducts of either Case 1 or 2, and neither gall bladder showed cholecystitis.

Case 1 had, to complicate matters, an unusually labile emotional picture, and after surgery she was recognized to have a convulsive disorder. It is not uncommon for sickle cell disease patients to have neurological signs or abnormal electroencephalograms, but in this case one must wonder if anti-convulsants were of greater value in controlling the patient's complaints than surgery. It is difficult to say whether Case 1 had seizure equivalents or so-called "abdominal epilepsy" secondary to sickle cell disease with intra-cranial thromboses or anoxia, but the follow-up history is at least suggestive of this.

Case 3 exemplified the unusual problem of a child with a chronic Salmonella septicemia of at least six months duration with no Salmonella demonstrable in the stools during the 3 months hospitalization prior to cholecystectomy. Possible sources suggested for this sepsis included endocarditis, osteomyelitis, or a localized abscess such as one in the brain, liver, or spleen. The only abnormality of the gall bladder was its enlargement and failure to contract immediately to a fatty meal stimulus. Actually with normal

TABLE I

Case Description

CASE	#1 C.H.	#2 A.T.	#3 D.L.	#4 R.D.
A. History				
Sex	F	M	M	M
Age	7 yr.	12 yr.	3 yr.	8 yr.
Color	C	C	W	W
Blood Dyscrasia	+	+	−	−
Specific food intolerance	−	−	−	−
Nausea	−	−	+	+
Vomiting	−	−	+	+
Diarrhea	−	−	+	−
Constipation	+	−	−	+
Abdominal pain	+	+	−	+
Past jaundice	+	+	−	−
Light stool	−	−	−	−
B. Physical examination				
Fever	−	+	+	+
Jaundice	+	+	−	−
Hepatomegaly	+	+	+	−
Splenomegaly	−	−	+	−
Abdominal mass	−	−	−	−
Abdominal tenderness	+	+	+	+
Associated infection				
C. Laboratory				
Moderate anemia (>8 Gm Hgb)	+	+	−	−
Blood dyscrasia	+	+	−	−
Leukocytosis (>13,000 WBC/mm³)	−	+	+	+
Acholic stool	−	−	−	−
Stool culture	0	0	−	−
Liver tests				
Ceph floc	0	4+	3+	−
Thymol turbidity	0	−	−	−
Direct bilirubin	0	0.8 mg %	−	−
Indirect bilirubin	0	7.2 mg %	−	−
Alk. phos.	0	−	−	0
Flat plate abdomen	+	+	−	+
Duodenal drainage	0	0	−	−
Cholangiogram	+	+	+ ; −	+

Symbols: + Abnormal history, physical finding, or laboratory test. − Normal by history, physical examination or laboratory test. 0 Test not performed.

stool culture, normal duodenal drainage, and a nonspecific history and physical examination, acute cholecystitis was indeed unlikely and surgery was performed with more hope than conviction. Bonta et al. in their case report recently described a case of Salmonella cholecystitis in a child and emphasized the extreme rarity of this entity today[3].

Case 4 is of interest as an illustration of a probable generalized sepsis producing acute meningitis, acute cholecystitis, acute pyelonephritis, and questionably significant peri-appendicitis. Antibiotic therapy was adequate in treating the meningitis. Gall bladder disease was suspected when, as the meningitis improved, there was persisting vomiting, right upper quadrant tenderness, and abdominal x-rays revealed a saccular mass producing partial obstruction of the third part of the duodenum by compression. At first it was feared that the vomiting and melena represented either a primary neurological complication of a subdural effusion or a brain abscess, or was a gastro-intestinal complication such as a Cushing-Rokitansky ulcer secondary to the intracranial infection. Although pathologically described as acute cholecystitis, the clinical picture is more that of acute distension of the gall bladder described by Forshall, et al.[4], and by Gross[5]. These authors suggest that this entity may be produced by compression of the cystic duct by an enlarged node. Unfortunately, no such node was looked for or found at surgery. In Case 4 intestinal parasites were found of which Trichiuris and Ascaris have both been implicated in past reports of gall bladder disease in children[4, 6]. Neither parasite was considered of etiologic significance in this patient's gall bladder disease.

All four cases had associated infections on hospital admission, and in Case 4 this was considered significant in association with the gall bladder disease. Appendicitis was not associated in any case.

The signs, symptoms, and laboratory evidence of gall bladder disease in infancy and childhood will be presented in another paper together with a review of the literature.

SUMMARY

Within the past 1½ years 4 cholecystectomies have been performed in children ranging from 3–12 years of age at Children's Hospital of the D. C. for probable gall bladder disease. Pathologically, 2 of these cases had cholelithiasis associated with severe sickle cell disease; one had acute cholecystitis and marked distension of the gall bladder associated with a bacterial meningitis and pyelonephritis; and one child with a chronic Salmonella septicemia had a normal gall bladder.

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Appreciation to Dr. Isidore Lattman is expressed for x-ray films and interpretations.

HERPES SIMPLEX

A Case Report Of A Primary Facial Lesion with Discussion of Laboratory Diagnosis*

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The herpes simplex virus first came under scrutiny as an etiological agent in human illness in 1912 when Gruter[1] associated it with herpetic keratitis. In 1919, infection of the labia by this virus was described by Lowenstein[2]. The herpes simplex virus was then shown to be a cause of gingivostomatitis in children by Dodd, et al.[3] in 1938. Burnet and Williams[4] confirmed this finding the following year and offered serological evidence to support the fact that the herpes simplex virus caused illness in humans. Since these early reports, a rather extensive literature has developed on the laboratory means of diagnosis of the disease, characteristics of the virus, epidemiology, and description of the various types of clinical manifestations[5-16].

The present report will describe a facial lesion which is unusual in that it occurred as a primary infection. In addition, a description of present day methods of laboratory diagnosis of infection due to the herpes simplex virus will be included.

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CASE REPORT

K. V., a 6 year old boy was first seen at The Clinical Center of The National Institutes of Health on October 12, 1955. On October 2 he had had an illness characterized by cough, rhinorrhea, and conjunctival erythema which had lasted for about 3 days. On October 6 a small red papule appeared on his right cheek in an area not known to have been previously traumatized. The following morning it contained clear fluid and looked like an ordinary "blister". That evening several smaller vesicles were noted around the central original one. Two days later he was seen by his private physician at which time the examination was negative except for the "crop of vesicles" on the right cheek. On October 10 the vesicles began to seep clear fluid and the central area of the lesion became crusted.

There was no fever associated with this lesion, and there were only mild, if any constitutional symptoms. The patient did not have vesicles within his mouth during this illness, nor had any been observed previously.

The physical examination was completely within normal limits except for the lesion on the right cheek (Figure 1). The entire lesion which was four centimeters in diameter was composed of several small peripheral vesicles which were oozing clear fluid and the center of which had a crusted area. There was a slightly erythematous base. A small amount of purulent material was expressed from under one corner of the crusted portion of the lesion.

The peripheral white blood cell count was 5,300 with 46 per cent polymorphonuclear cells, 47 per cent lymphocytes, 1 per cent monocytes, and 5 per cent eosinophils. The erythrocyte sedimentation rate, hemoglobin, and hematocrit were normal. Bacterial and fungal cultures of the lesion and throat did not reveal any pathogens.

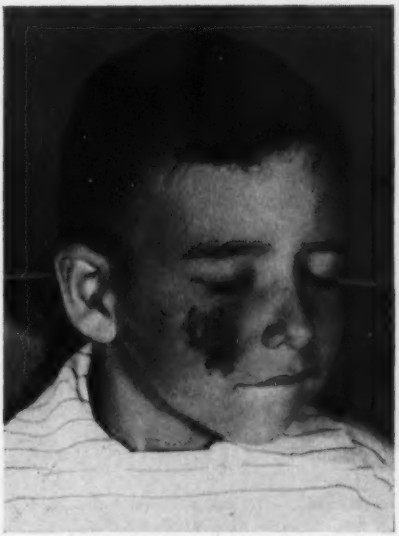

FIG. 1. Photograph of facial lesion due to primary infection with the herpes simplex virus.

The diagnostic virus isolation techniques and laboratory methods are described in detail in the following section.

Course: The acute vesicular lesions cleared up over a period of ten days. The crusted central portion remained an additional week. The patient was seen again two months after the first examination. At that time several small pitted depressions could be noted in the skin, and the circular area retained a residual minimal erythematous appearance.

LABORATORY METHODS

Aliquots of the washings from swabs of the lesion and of the throat were inoculated into tissue culture roller tubes containing HeLa, monkey kidney, and human embryo fibroblast cells. Within 24 hours, characteristic herpetic cytopathogenic effects were apparent in the HeLa cultures inoculated with material from the cutaneous lesion (Figure 2 and 3). Positive results from washings of the swab of the skin lesion were apparent in the monkey kidney and human embryo fibroblast cells somewhat later (48–72 hours). Washings from swabs of the throat were negative in all tissues.

FIG. 2. Photograph of normal HeLa cells

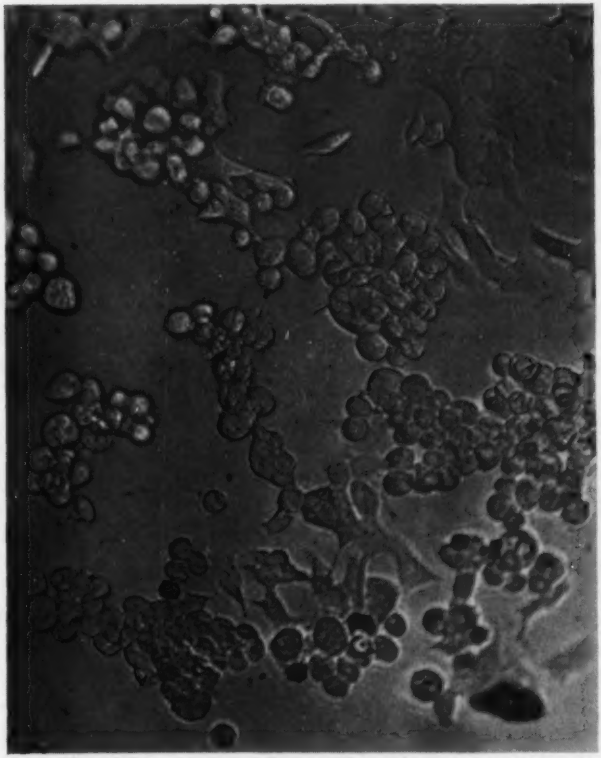

FIG. 3. Photograph of the cytopathogenic effect of the herpes simplex virus in HeLa tissue culture cells.

All subsequent tissue culture work was performed in HeLa cells which present optimal growing conditions for this virus. The virus was serially passed in 10-fold dilutions 8 times in HeLa cells, the cytopathogenic effect being easily evident within 24 hours.

Rabbit antiserum was prepared against the virus isolated from the patient and [12] used in tissue culture neutralization tests against a standard herpes simplex virus (strain 6116). This serum showed complete protection against the virus in tissue culture at a dilution of 1:4 and partial protection at a dilution of 1:8. Normal control rabbit serum showed no neutralizing effect in tissue culture. Sera from the patient taken on the fourth and the sixteenth days from the onset of illness were also tested in tissue culture neutralization against herpes simplex virus, strain 6116. The acute serum showed no inhibitory effect while a protective titer of 1:8 was present in the convalescent serum.

Material from the facial lesion was inoculated into the cornea of a rabbit. Within 72 hours an inflammatory lesion of the cornea became evident. Four days later, the animal became quite ill and showed signs of muscle paralysis. Material from the

eye was passed to suckling mice and produced illness characteristic of herpes infection.

Suckling mice were also inoculated intraperitoneally directly with material from the lesion[17]. Signs consistent with herpes simplex infection became evident in them within 3 days.

A complement fixation test was performed on the acute and convalescent sera according to the method of Dascomb, Adair, and Rogers[14]*. The acute serum exhibited a titer of less than 1:4 while the convalescent serum showed a titer of 1:128 or greater against the herpes simplex antigen. This is consistent with a primary herpetic infection.

DISCUSSION

The host-parasite relationship of the herpes simplex virus may be considered to have three phases, roughly correlated with age and immunity of the host. 1) During the first six months of life most infants are protected by passively transferred neutralizing antibodies from the mother[18]. 2) From infancy up to about 5 years of age a vast majority of children experience a primary infection with the virus. The primary infection in a majority of instances is a subclinical one. In a 1000 family survey in England it was found that only 9 per cent of the children who developed antibodies against the virus had had previous clinical illness ascribable to the herpes simplex virus[19]. The mucous membranes of the mouth or of the genital tract are the usual site for the primary infections. Much less commonly, the primary lesion will affect previously damaged or traumatized skin, i.e., in areas of burns, atopic dermatitis, intertrigo, or eczema[13, 16]. The disease may also manifest itself as a meningoencephalitis or as an infection of viscera, including the liver. 3) Recurrent herpetic infection occurs in individuals who have circulating antibodies. The current concept is that, following the primary infection, the virus remains clinically latent in the tissues and constantly stimulates immunity. Then at varying intervals, whenever this balance is upset by such factors as fever, sunburn, emotional disturbances, recurrent herpes becomes manifest[13, 16]. This is most commonly apparent as the troublesome fever blister or as genital herpes. The lesion is unique in that ordinarily there are several grouped vesicles on an erythematous base.

The case described here represents a primary infection by the standards above discussed in that the patient did not have either neutralizing or complement fixing antibodies present in the acute serum. However, serum taken 16 days after onset of the facial lesion showed significant amounts of both antibodies.

Considering the age of the patient and that the primary infection would have had to have occurred within the preceding 5½ years, circulating anti-

* Performed at the Walter Reed Institute of Research, Department of Viral Diseases, through the courtesy of Captain Harry M. Meyer, Jr., M.C.

bodies should have been present in the acute serum were the present lesion a recurrent one. The lesion is unusual in that it occurred in an area of skin previously undamaged. Moreover, there was no history of preceding skin involvement of this area that might have represented a herpetic infection. The other interesting feature of this case is that the lesion with grouped vesicles on an erythematous base is one which is usually said to be characteristic of the recurrent type of infection.

DIFFERENTIAL DIAGNOSIS

A facial herpetic lesion of the type described here must be differentiated from those caused by other viruses as well as those due to bacterial and fungal agents.

Impetigo contagiosa might be confused with such a herpetic lesion especially if the latter were secondarily infected by bacteria.

Fungal infections of the face might produce a similar picture early in the course of the disease. Here, cultures or direct examination of a potassium hydroxide preparation should be sufficient to make the differentiation.

Although uncommon, autoinoculation of vaccinia virus from a vaccination site or from contact with a recently vaccinated person could produce a vesicular lesion similar to this.

Vesicular lesions of the face may also be a manifestation of contact dermatitis caused by chemicals, plants, external irritants, and various other excitants.

TREATMENT

There is no specific therapy for lesions due to the herpes simplex virus. Facial cleanliness to prevent secondary bacterial infection is indicated. If secondary infection does occur, prompt antibiotic therapy should be instituted.

SUMMARY

A facial lesion occurring in a 6 year old child was due to a primary infection with herpes simplex virus in present day methods of isolation and identification of the herpes simplex virus emphasis is being placed on tissue-culture methods.

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DIAGNOSTIC BRIEF

George J. Cohen, M.D.

Slipped Femoral Epiphysis

To minimize permanent hip disability, separation or slipping of the femoral capital epiphysis must be corrected early and definitively. Obviously, this presupposes early diagnosis.

Slipped femoral epiphysis or epiphyseolysis is a fairly common cause of limp and pain during adolescence. It is more common in boys than girls by a ratio of four to one. Classically, the child is either obese with a Fröhlich type habitus, or else is quite linear and growing rapidly. There may be a history of trauma, but usually it is insignificant.

Although the symptoms may start abruptly and severely, the typical onset is so insidious that it is often ignored by parents and physician until deformity is obvious. The earliest symptom is usually a limp with pain in the hip or in the knee. X-ray at this stage often shows nothing, or at most, only widening of the epiphyseal line which can easily be overlooked. Lateral views of the hip may show slipping earlier than antero-posterior views. However, it is the physical examination which very frequently establishes the diagnosis. If the patient lies prone with his knees flexed to ninety degrees, definite painful limitation of internal rotation of the hip may be demonstrated. If the patient continues to bear weight on the affected leg, he may acquire more limp, more pain, and shortening and external rotation of that femur due to forward and upward displacement of the femoral neck on its head. At this point both clinical and x-ray diagnosis are all too apparent.

Although closed reduction and bed rest were advised by early writers, these methods of treatment seem quite unsatisfactory. Further slipping has often occurred with the patient at complete bed rest. The ideal therapy is fixation of the epiphysis with an orthopedic nail; the earlier the fixation is accomplished, the easier the job and the better the result.

In summary, any adolescent child who has a painful limp should be tested for limitation of internal rotation of the hip and should have lateral as well as antero-posterior x-rays taken of his hips. Once a diagnosis of epiphyseolysis is made, the epiphysis should be nailed without delay.

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